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Diagnostic endoscopy and infertility

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This opinion paper represents an evidence-based view on the role of diagnostic endoscopy in infertility. The authors strongly believe that patients with infertility problems and research in reproductive medicine are best served in centers of reproductive medicine with a joint diagnostic and therapeutic expertise in both reproductive surgery and medically assisted reproduction. Such a system has been developed at the Division of Reproductive Medicine at Leuven University Hospitals since the 1970s. This effort has been awarded with an ISO 9001-2000 certificate for high quality management of infertile couples in 2004 (first award within the Belgium-Netherlands-Luxemburg European area). The European sub specialization program in reproductive medicine, developed by the European Society of Human Reproduction and Embryology (ESHRE) together with the European Board and College of Obstetrics and Gynecology (EBCOG) is also based on joint training in reproductive surgery and medically assisted reproduction. The Division of Reproductive Medicine at Leuven University Hospitals has been the first EU center of reproductive medicine accredited by ESHRE and EBCOG for sub specialization training in reproductive medicine since 2008.

Relevant WHO definitions

In the context of this paper it is important to define reproductive surgery in the context of other clinical management in reproductive medicine, including medically assisted reproduction and assisted reproductive technology. Since 2009, these terms have been clearly defined by WHO-ICMART [1].

Reproductive surgery is defined as all surgical procedures carried out to diagnose, conserve, correct, and/or improve reproductive function.

Medically assisted reproduction (MAR) is defined as reproduction brought about through ovulation induction, ovarian stimulation, ovulation triggering (HCG), sperm insemination (intra-uterine, intra-cervical, intra-vaginal) or assisted reproductive technology (ART) procedures.

ART is defined as all treatments or procedures including *in vitro* handling of both human oocytes and sperm or embryos, for the purpose of establishing a pregnancy, and includes : IVF/ICSI, GIFT, ZIFT, egg/embryo donation, gamete/embryo cryopreservation. It excludes sperm insemination.

Indications for hysteroscopy

A hysteroscopy can be done for the evaluation or treatment of uterine cavity, tubal ostia and endocervical canal in women with uterine bleeding disorders, Müllerian tract anomalies, retained IUDs or other foreign bodies, retained products of conception, desire for sterilization, recurrent miscarriage and subfertility. A diagnostic hysteroscopy serves to evaluate the uterine cavity only, and can be done as an out-patient procedure, without sedation. An operative hysteroscopy allows surgical treatment of detected intra-uterine pathology, is usually done as day care surgery under general sedation, but new equipment increasingly allows minor hysteroscopy surgery without sedation on an out-patient basis.

A hysteroscopy is one of the techniques allowing diagnostic evaluation of the intrauterine cavity in infertile

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women. Other techniques include transvaginal sonography (TVS), possibly with the use of contrast fluid (Saline infusion sonography (SIS), Gel infusion sonography (GIS), Hydro foam sonography [HYFOSY]); and hysterosalpingography (HSG).

These indications have been addressed recently in a Cochrane review [2] and are summarized below.

Spontaneous conception

Hysteroscopic removal of endometrial polyps, with a diameter of 16 mm detected by TVS doubles the pregnancy rate when compared to diagnostic hysteroscopy with polyp biopsy in patients treated with intra-uterine insemination (IUI, starting 3 months after surgery (RR 2.3 ; 95 % CI 1.6 to 3.2) [3].

Hysteroscopic removal of submucous (SM) myomas. In patients with one SM fibroid < 4 cm has been shown to have a marginally significant benefit when compared to expectant management (RR 1.9 ; 95 % CI 1.0 to 3.7) [4].

Before treatment with ART

In patients with at least two failed IVF attempts, hysteroscopy in the cycle preceding subsequent IVF attempt nearly doubles pregnancy rate when compared to direct IVF (RR 1.7 ; 95 % CI 1.5 to 2.0) [2, 5-7]. This beneficial treatment effect does not depend on the presence or absence of intrauterine pathology [2].

Hysteroscopic treatment of intrauterine adhesions (Ashermann syndrome)

Hysteroscopic lysis of intrauterine adhesions (IUAs) is the only reasonable treatment option for women who wish to become pregnant. Hysteroscopic lysis of adhesions (scissors, electrosurgery, and laser) can restore size and shape of uterine cavity, but significantly obliterated cavities may require multiple procedures [8]. Treatments outcomes are difficult to assess, but the overall intrauterine (IU) pregnancy rates vary between 22-45 %, whereas the live birth rates (LBRs) vary between 28-32 %. After surgery, there is an increased risk of placenta accreta and subsequent blood loss, transfusion, and hysterectomy [9]. Practical aspects of this surgery have been recently summarized in the AAGL Practice Guidelines for the management of intrauterine synechiae [10]. Whereas there is no evidence to support the use of blind cervical probing or blind dilation and curettage, direct visualization of the uterine cavity at hysteroscopy in conjunction with a tool for adhesiolysis is the treatment of choice for IUAs [10]. Guidance by external imaging techniques or laparoscopy should be encouraged as this may minimize consequences if perforation occurs in selected patients with severe intrauterine adhesions, although there is no evidence that such guidance is effective in the complete prevention of uterine perforation or in the improvement of clinical outcome [10]. Postoperative use of IU Barriers (hyaluronic acid ; auto-cross-linked hyaluronic acid gel), or postoperative estrogen treatment, with or without a progestin, can possibly reduce the recurrence of IUAs, but has not demonstrated benefit with respect to reproductive outcome [10]. There is no evidence that antibiotics used pre-, intra-, or postoperatively improve reproductive outcome [10]. Medications to improve vascular flow to the endometrium (aspirin, nitroglycerine or phosphodiesterase inhibitors) should only be used in research settings [10]. Progestin-releasing IUDs (suppressive endometrial effect), copper or T-shaped IUDs, or Foley catheters (risk for inflammation/infection) should not be inserted postoperatively [10]. It is recommended to do a postoperative follow-up hysteroscopic assessment of the uterine cavity [10].

Overall, in view of emerging evidence and the minimally invasive character of hysteroscopy, the use of diagnostic hysteroscopy should no longer be discouraged as a first line investigation [2], as stated in the NICE clinical guideline 156 on fertility assessment [11]. Indeed, hysteroscopy should be recommended in case of a suspected uterine cavity abnormality and prior to IVF [12].

Indications for diagnostic laparoscopy

A diagnostic laparoscopy is indicated for the investigation of tubal and pelvic function related to female infertility, in particular when associated with endometriosis or tubal disease. During day care surgery, a laparoscopy can be combined with a hysteroscopy and with tubal patency testing. Women who are thought to have comorbidities should be offered laparoscopy and dye so that tubal and other pelvic pathology can be assessed and treated at the same time [11]. According to the French guidelines, laparoscopy should be recommended in case of suspected pelvic pathology due to ruptured appendicitis ; prior pelvic surgery ; suspicion of PID ; suspicion of pelvic endometriosis ; positive testing for C. trachomatis ; presence of hydrosalpinx on ultrasound [12] other conditions that suggest presence of pelvic pathology. A normal HSG reasonably excludes tubal occlusion whereas an abnormal HSG should be regarded as a clear-cut indication for a laparoscopy and dye test to exclude, diagnose or treat tubal pathology. The diagnosis of true unexplained subfertility should never be established without a normal diagnostic laparoscopy [13].

A diagnostic laparoscopy before treatment of IUI for unexplained or mild male factor subfertility is a matter of debate [14, 15] and should be discussed with the couple. Indirect evidence supports that pregnancy rates after IUI in women with minimal-mild endometriosis, known to be lower than in women with unexplained infertility, can

be improved by laparoscopic surgery for endometriosis before the start of IUI [15]. Indeed, similar reproductive outcome was observed after ovarian stimulation and IUI in women with unexplained infertility and in women with recently surgically treated minimal/mild endometriosis with respect to the ppregnancy rate per cycle (20 %), the cumulative live birth rate (67 %) after 4 cycles, and the multiple pregnancy rate (< 10%). However, in another RCT reallocation study [14], aimed at evaluating the role of laparoscopy in patients scheduled for IUI treatment, no benefit of laparoscopy was observed. In order to resolve this question, an RCT is needed to test the hypothesis that surgical excision of endometriosis before IUI increases the pregnancy rate during IUI treatment when compared to diagnostic laparoscopy alone.

Diagnostic laparoscopy is not a panaceum [16-18] : if a 100 % certainty level about tubal integrity is requested, there will be inflation of costs and an increase in the pool of women with a diagnosis of minimal pathology of questionable prognostic significance [19]. However, ART is not a panaceum either [16-18], since a more extensive use of 1481 ART cycles per million per year would result in only 47 % live birth rates [19].

In comparison to standard laparoscopy, transvaginal hydrolaparoscopy (THL) [20, 21] has been proposed as a safe, efficacious and validated diagnostic technique in women with unexplained infertility and for diagnosis of endometriosis. However, 15 years after the introduction of THL, it is still not routinely used in the majority of centers of reproductive medicine. We hypothesize that the following reasons are responsible for the lack of implementation of THL in routine reproductive medicine. Firstly, THL requires specific technical skills, with a learning curve which requires a sufficiently high number of patients, making it difficult for clinicians in small centers to gain sufficient experience and expertise. Secondly, in spite of earlier claims that THL can easily be done without general anesthesia, in fact conscious sedation is needed during THL, which makes it day care surgery, just like standard laparoscopy. Thirdly, THL is, just like standard laparoscopy, associated with a low (<1%) risk for bowel injury. Fourthly, equivalence or superiority of THL versus hysterosalpingography (HSG) as first line investigation in infertile women has not been demonstrated [21]. Fifthly, advanced ultrasound hydrosonographic techniques can be increasingly considered as valid alternatives for THL and for classical HSG to visualize both uterine cavity and tubal patency [22]. Sixthly, although THL allows visualization of filmy free floating adhesions and micropolypoidal lesions on the ovarian surface, this observation has unclear clinical significance. Seventhly, even in expert hands, THL does not allow complete pelvic evaluation since it is impossible to have the panoramic pelvic view available during standard laparoscopy. Indeed, during THL it is not possible to inspect the vesico-uterine compartment, and only partial evaluation of uterosacral/rectal areas for endometriosis is possible. Eighthly, therapeutic surgery is impossible in routine practice, although ovarian drilling in patients with PCOS has been proposed.

At the Leuven University Fertility Center, we have adopted the following role for diagnostic endoscopy (diagnostic hysteroscopy, laparoscopy and tubal patency testing) in our patients with infertility. Endoscopy is always offered to women with pain or with an adnexal mass. Endoscopy is also proposed to women with a regular menstrual cycle whose partner has normal sperm quality, because 50 % has endometriosis [23] and surgery will increase the spontaneous pregnancy rate and reduce pain [24], and 40 % of those without endometriosis have other fertility-reducing pelvic pathology which may benefit from surgery [23]. Before IUI : we always propose diagnostic endoscopy as surgical treatment of minimal-mild endometriosis increases the spontaneous pregnancy rate and may improve reproductive outcome after IUI treatment.

Endometriosis

In women with endometriosis, indications for surgery include pain or infertility or both pain and infertility. Symptoms of pain and subfertility are often combined, but this aspect is underestimated in the literature where there is a tendency to dichotomize patient presenting complaints as either infertility or pain. However, the reproductive status of women with endometriosis may vary between active child wish, passive child wish (sometime in the future), incomplete child wish, and all these aspects relate to fertility and to infertility. Furthermore, some patients may be in too much pain to consider sexual intercourse and pregnancy before surgery, but may reconsider this after surgery when pain during intercourse and other pelvic pain has become tolerable allowing the idea of conception/pregnancy. For these reasons, in most women, endometriosis surgery is reproductive surgery, as defined by WHO-ICMART [1]. Women with endometriosis are entitled to receive reconstructive reproductive surgery ; a non-reconstructive approach (hysterectomy) is only justified in women with « truly and definitively completed » child wish. All women with endometriosis have the right to receive an integrated approach with respect to both their reproductive wishes + the possible presence of pelvic pain, and a plan of action should be discussed with these patients taking into account both issues.

Overall, laparoscopic treatment of both minimal-mild endometriosis [24, 25] and moderate-severe endometriosis [11] improves fertility in women with endometriosis-

associated subfertility. In infertile women with ovarian endometrioma undergoing surgery, clinicians should perform excision of the endometrioma capsule, instead of drainage and electrocoagulation of the endometrioma wall, to increase the spontaneous pregnancy rate [11, 25]. The management of an endometrioma before ART treatment is more controversial. In the context of treatment with ART, there is no evidence that surgery, medical treatment, combination therapy or no treatment improve reproductive outcome after ART among women with endometriomata, prior to undergoing ART cycles [26]. For women who are found to have an asymptomatic endometrioma and who are planning to undergo IVF/ICSI, there is insufficient evidence to suggest that removal of the endometrioma will improve IVF success rates [27]. However, if the endometrioma is large (>4 cm), surgery should be considered to confirm the diagnosis histologically, to improve access to follicles during oocyte retrieval, and possibly to improve ovarian response [27]. Patients should be made aware that extensive ovarian surgery could compromise ovarian function and diminish the response to ovarian stimulation [27]. Further RCTs of management of endometrioma in women undergoing ART are required. The best surgical approach to deep endometriosis in women with infertility is unclear [25, 28]. However, in multidisciplinary centers of expertise, excellent reproductive outcome has been documented after surgery for deep endometriosis, also when laparoscopic bowel resection with anastomosis [29-31].

Conflicts of interest : The authors have non conflicts of interest.

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